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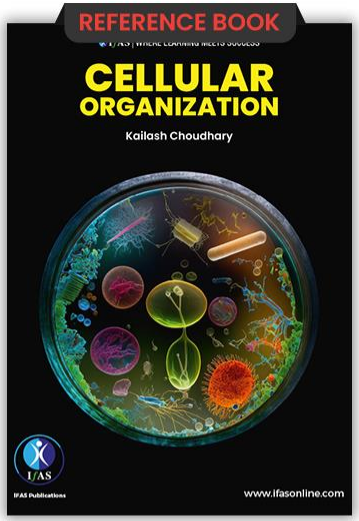
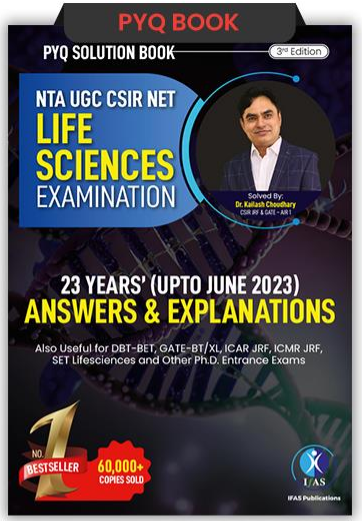
CSIR NET – Life Science

Unit 2: Cellular Organization

L10 **Nucleus**

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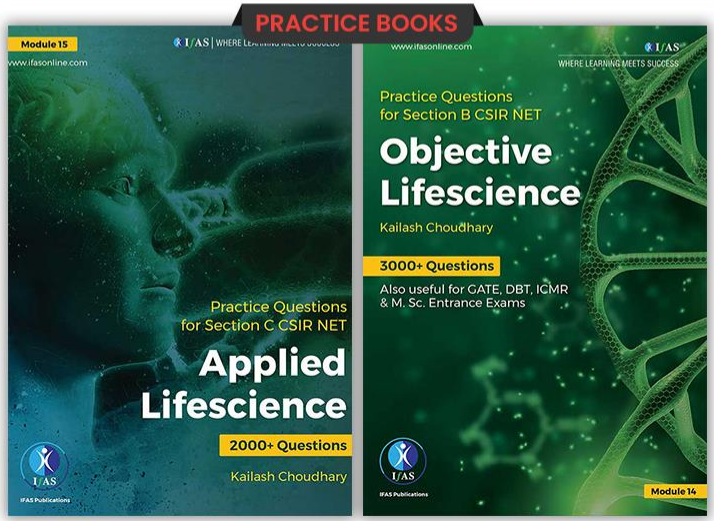

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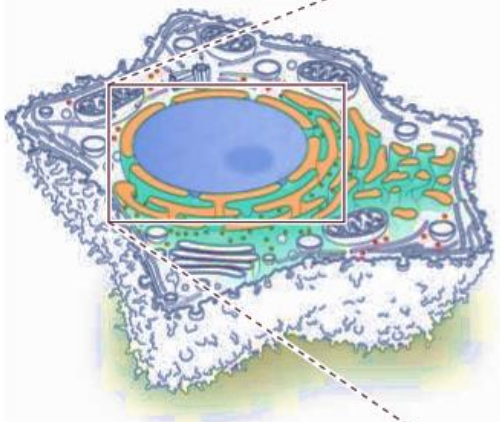
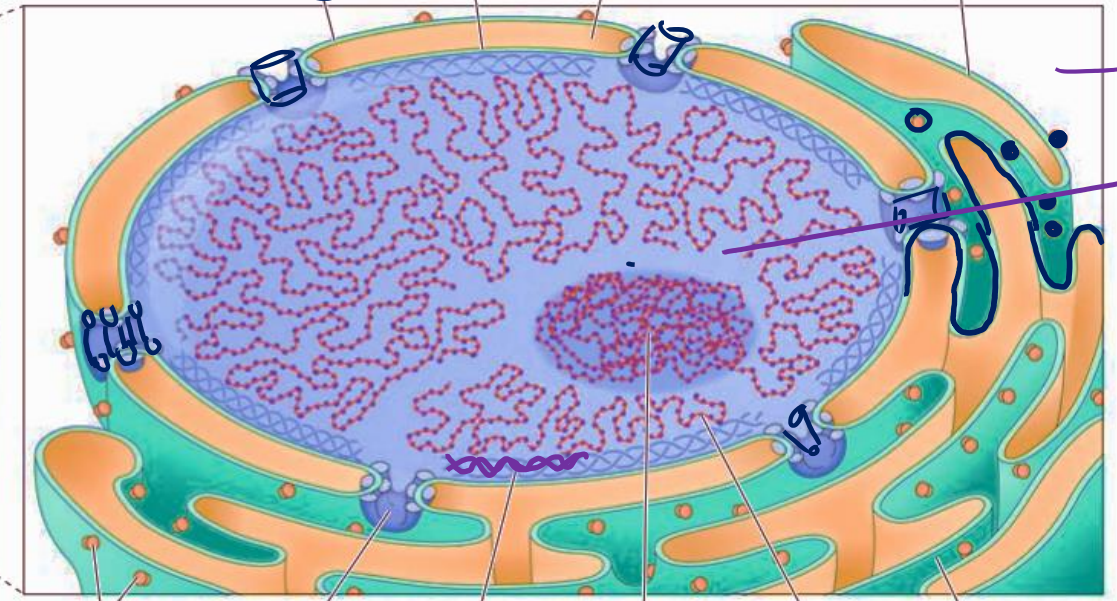
Points to be covered in this Lecture

- Nucleus structure
- Nuclear pore complex
- Protein targeting to nucleus
- Nucleolus and Nuclear bodies

Nucleus

- Double membranous Sr.
- outer membrane is continuous with RER





9nm Diameter - Always open
Can Expand Upto 23-30 nm Diameter

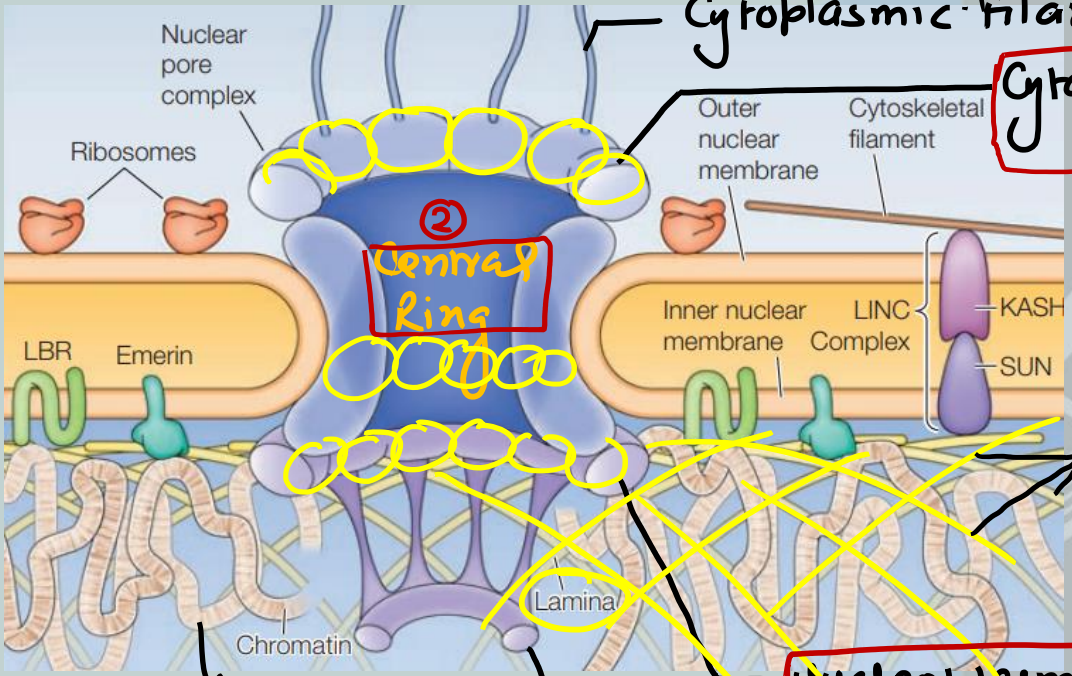
maintain Shape of Nucleus

The nuclear envelope

- An electron micrograph of a nucleus. The inner and outer nuclear membranes are joined at nuclear pore complexes (arrows).
- An electron micrograph illustrating the continuity of the outer nuclear membrane with the endoplasmic reticulum.
- The inner nuclear membrane is lined by the nuclear lamina, which serves as an attachment site for chromatin.
- The nuclear lamina is composed of 60- to 80-kilodalton (kd) fibrous proteins called lamins, along with associated proteins

↳ maintain shape

Nuclear pore complexes → made up of 3 Ring Protein Consist of 8 Small Subunit



Cytoplasmic filament

Cytoplasmic Ring

② Central Ring

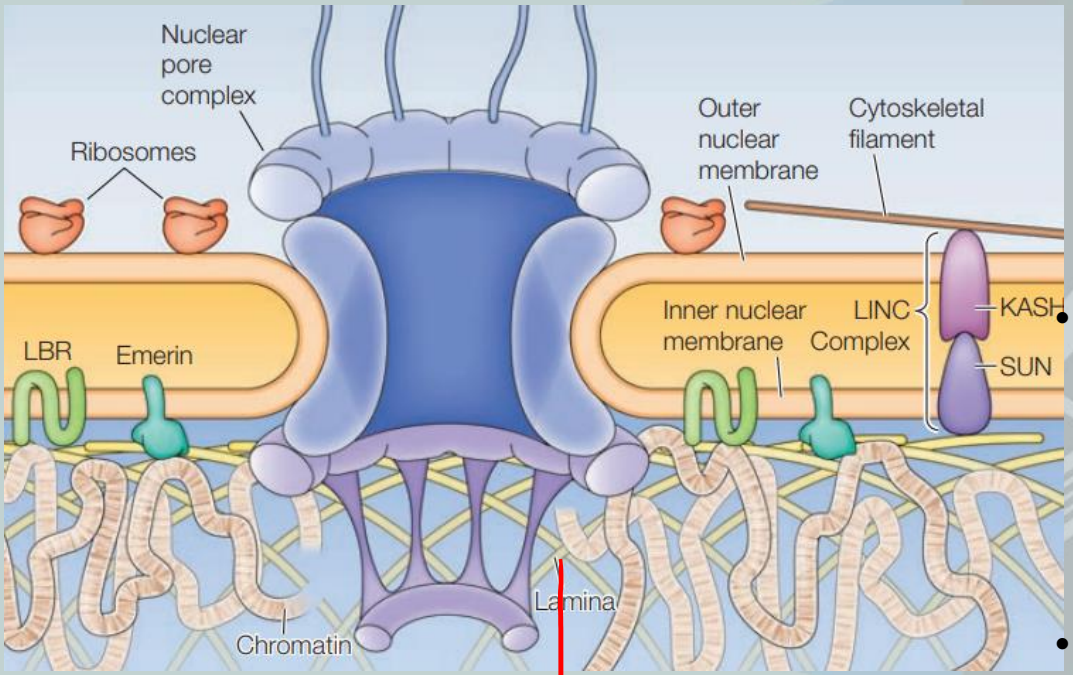
Nuclear Kamin A

- maintain shape of Nucleus
- Binds with Chromatin.

Chromatin

Nucleoplasmic ③ Ring

Nuclear Basket



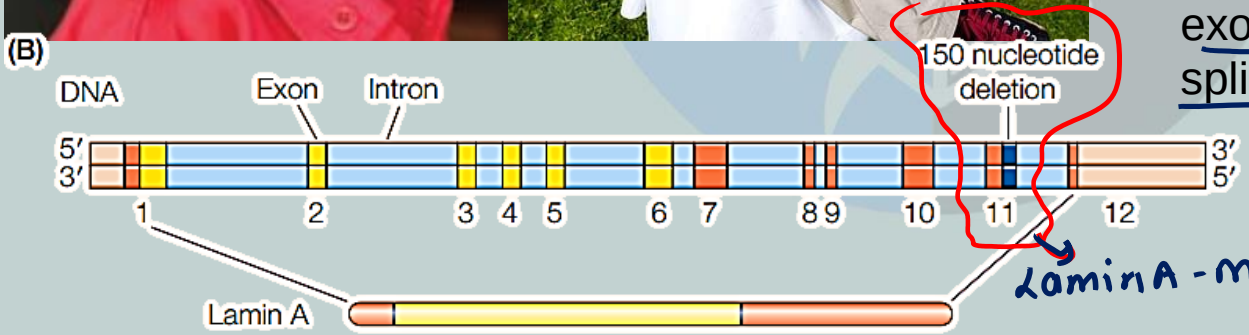
- The nuclear lamina The inner nuclear membrane contains several integral membrane proteins, such as emerin, the Lamin B receptor (LBR), and the SUN proteins, that interact with nuclear lamins.
- The SUN proteins bind the KASH proteins in the outer nuclear membrane, making up the LINC complex that connects the nuclear lamina to the cytoskeleton.
- The Lamins and inner nuclear membrane proteins also interact with chromatin.

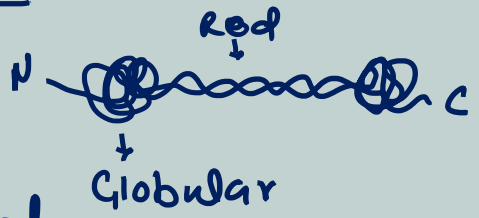
CELL BIOLOGY

A child with Hutchinson-Gilford progeria.

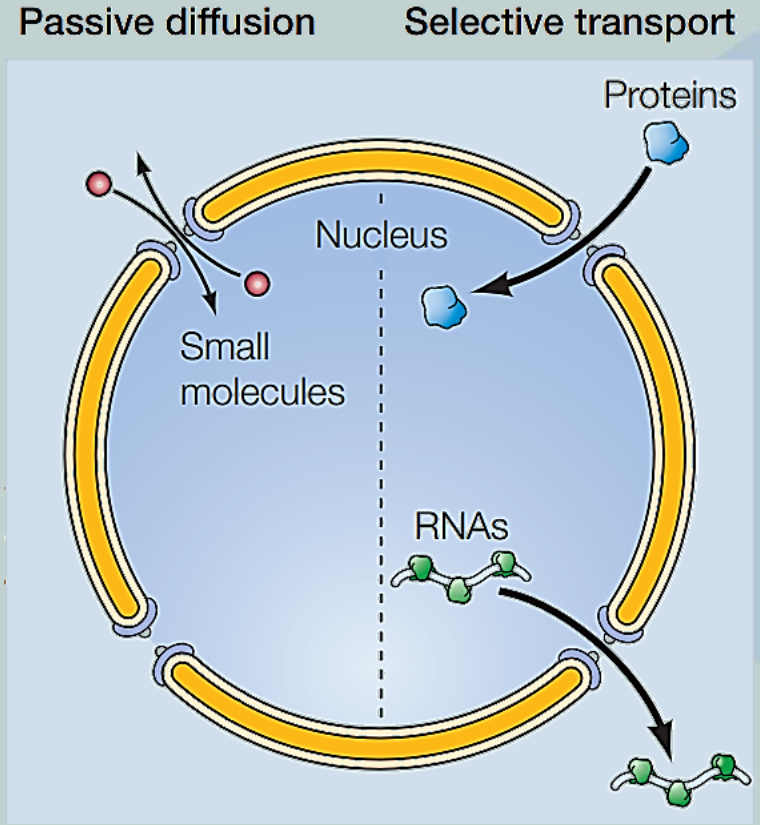
- (B) Diagram of the intron-exon structure of the LMNA gene and lamin A protein, with the globular domains indicated in red and the rod domains in yellow.

- The mRNA encoded by the mutant gene shown has a 150-basepair deletion (dark blue) in exon 11 as a result of aberrant splicing.





Molecular traffic through nuclear pore complexes



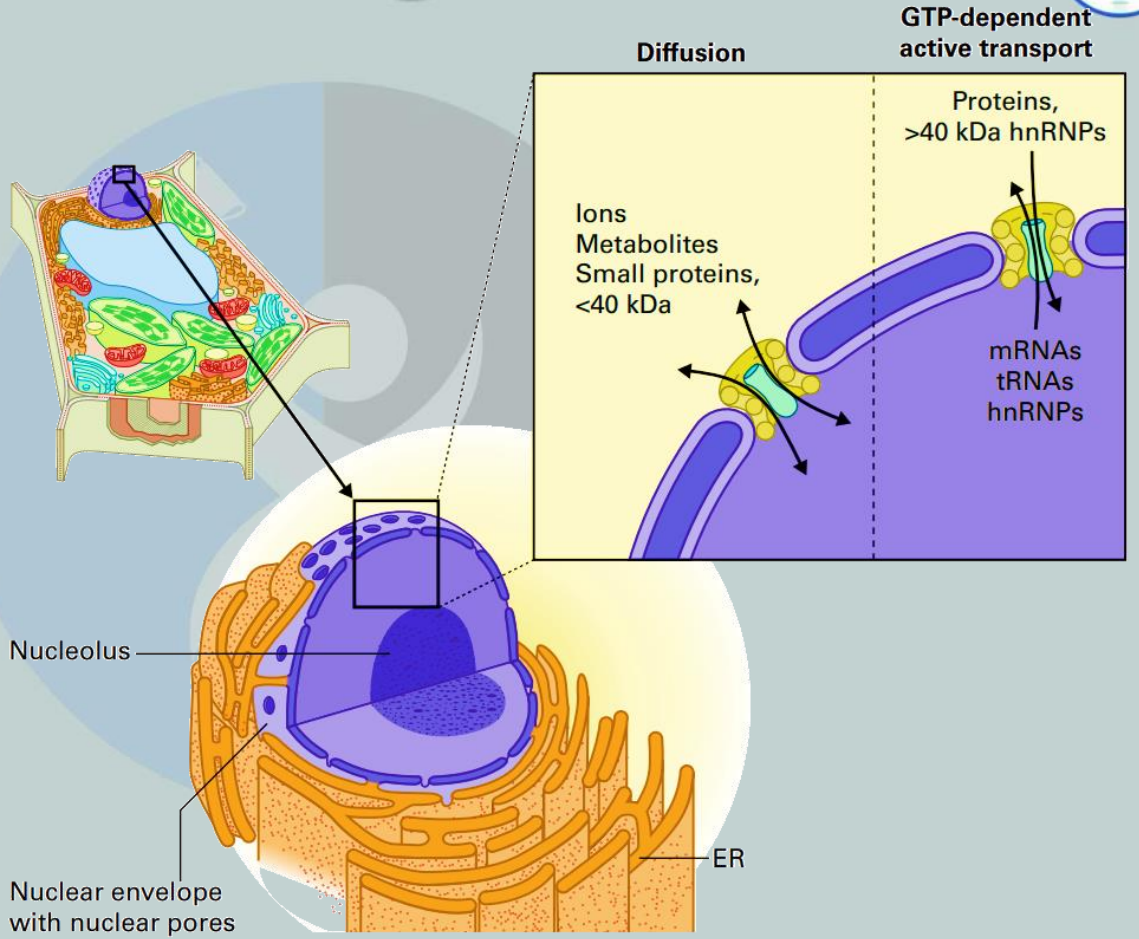
Molecular traffic through nuclear pore complexes

- Small molecules are able to pass freely through the nuclear pore complex by passive diffusion.
- In contrast, macromolecules (proteins and RNAs) are recognized by specific signals and selectively transported either from nucleus to cytoplasm or from cytoplasm to nucleus.

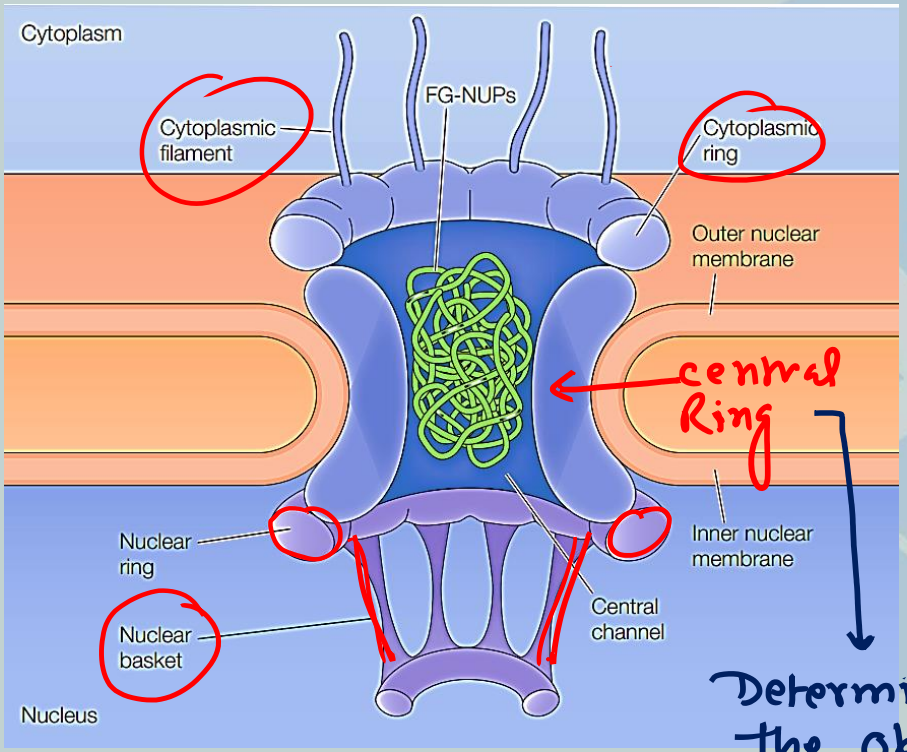
Nucleus structure

Protein transport into the nucleus by diffusion or by active → GTP-dependent transport.

✓ hnRNP, heterogeneous nuclear RNA-binding proteins



The nuclear pore complex



- The complex consists of an assembly of eight spokes attached to rings on the cytoplasmic and nuclear sides of the nuclear envelope.
- The spoke–ring assembly surrounds a central channel. Cytoplasmic filaments extend from the cytoplasmic ring, and filaments forming the nuclear basket extend from the nuclear ring.
- The central channel is lined by proteins (FG-NUPs) that regulate transport through the complex.

Determines the opening diameter of Nuclear pore

Nucleus

- Several million macromolecules selectively pass between the nucleus and the cytoplasm every minute
- They include histones, DNA polymerases, RNA polymerases, transcription factors, splicing factors, and many others
- These proteins contin specific amino acid sequences called nuclear localization signals (NLS), recognized by nuclear transport receptors that direct protein transport through the nuclear pore complex.

9mb.

- The first NLS mapped in detail by Alan Smith and colleagues in 1984

- In simian virus 40 (SV40) T antigen, a virus-encoded protein that initiates viral DNA replication in infected cells.
- T antigen is normally localized to the nucleus.

- The signal responsible for its nuclear localization was first identified by the finding that mutation of a single lysine residue prevents nuclear import, resulting instead in the accumulation of T antigen in the cytoplasm.

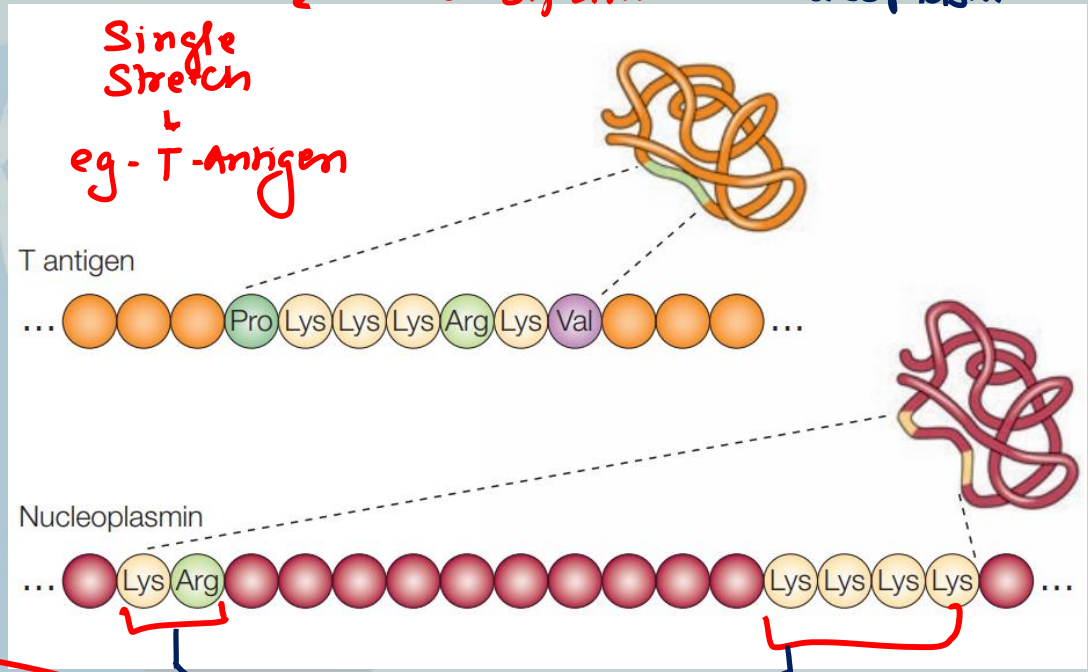
Nuclear localization signals

NLS → Bipartite → Nucleoplasmin

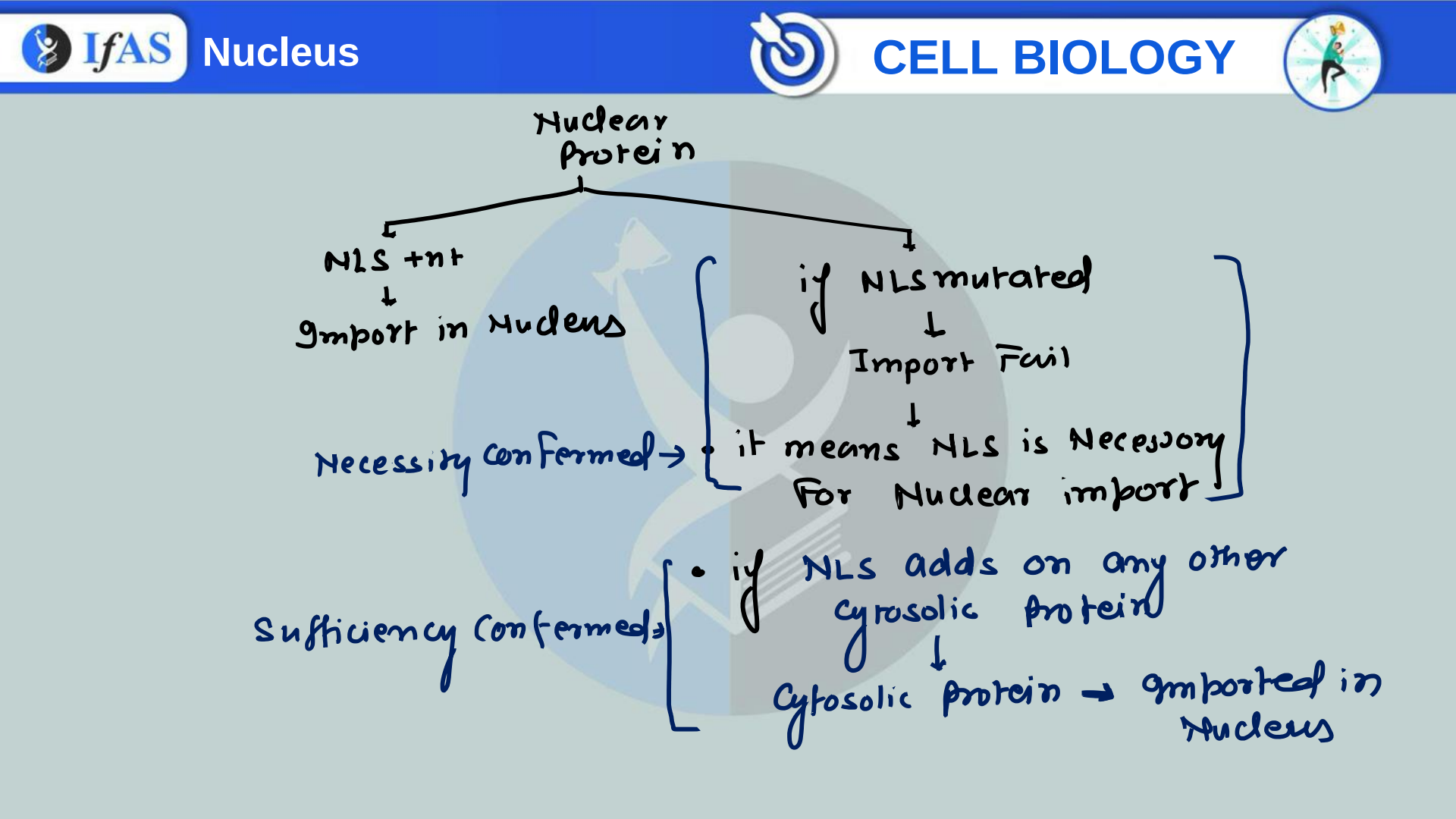
- The T antigen nuclear localization signal is a single stretch of amino acids.

Single Stretch → eg - T-Antigen

- In contrast, the nuclear localization signal of nucleoplasmin is bipartite, consisting of a Lys-Arg sequence, followed by a Lys-LysLys-Lys sequence located ten amino acids farther downstream



NLS Recognized by importin


Nuclear Protein
NLS +nt
↓
Import in Nucleus
if NLS mutated
↓
Import Fail
↓
it means NLS is Necessary For Nuclear import
Necessity Conformed →
Sufficiency Conformed →
if NLS adds on any other cytosolic protein
↓
Cytosolic protein → imported in Nucleus

nuclear export signals [NES] -> Recognized by exportin

- which are often rich in the hydrophobic amino acid leucine.]- Leu rich signal
- Like nuclear localization signals, nuclear export signals are recognized by receptors within the nucleus—exportins

Like importins, exportins are members of a family of nuclear transport receptors known as **karyopherins**

Karyopherin	Substrates
Import	
Importin	Proteins with a basic amino acid nuclear localization signal (e.g., nucleoplasmin)
Snurportin	snRNPs (U1, U2, U4, U5)
Transportin	mRNA binding proteins, ribosomal proteins
Importin7	Histone H1, ribosomal proteins
Export	
Crm1	Proteins with a leucine-rich nuclear export signal, snurportin, snRNAs, ribosomal subunits
Exportin-t	tRNAs
Exportin5	miRNAs

Karyopherin	Substrates
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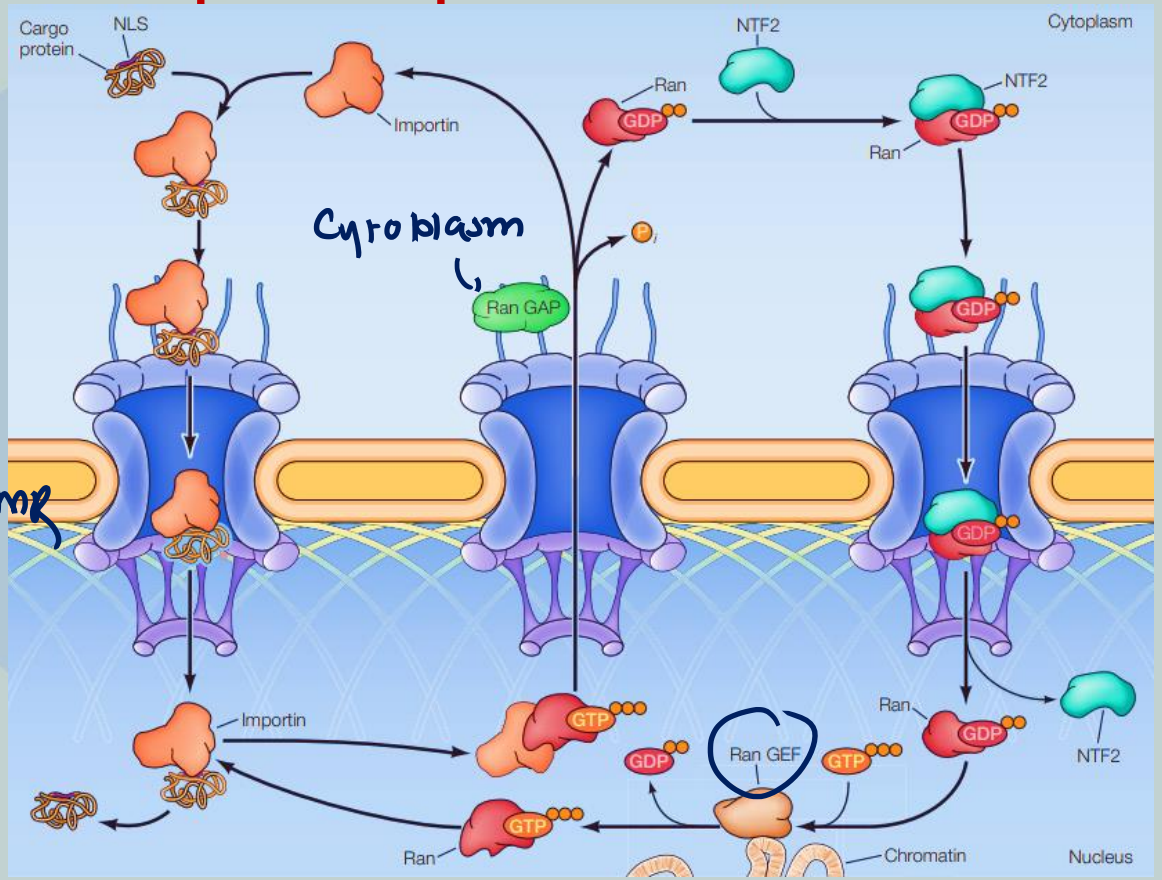
Exportin-t	tRNAs
Exportin5	miRNAs

Protein import through the nuclear pore complex

At the nuclear side of the envelope, Ran/GTP binds to the importin, disrupting the cargo/importin complex and releasing the cargo protein into the nucleus

Importins → CSIR/DBT/ICMR/RARC/SET

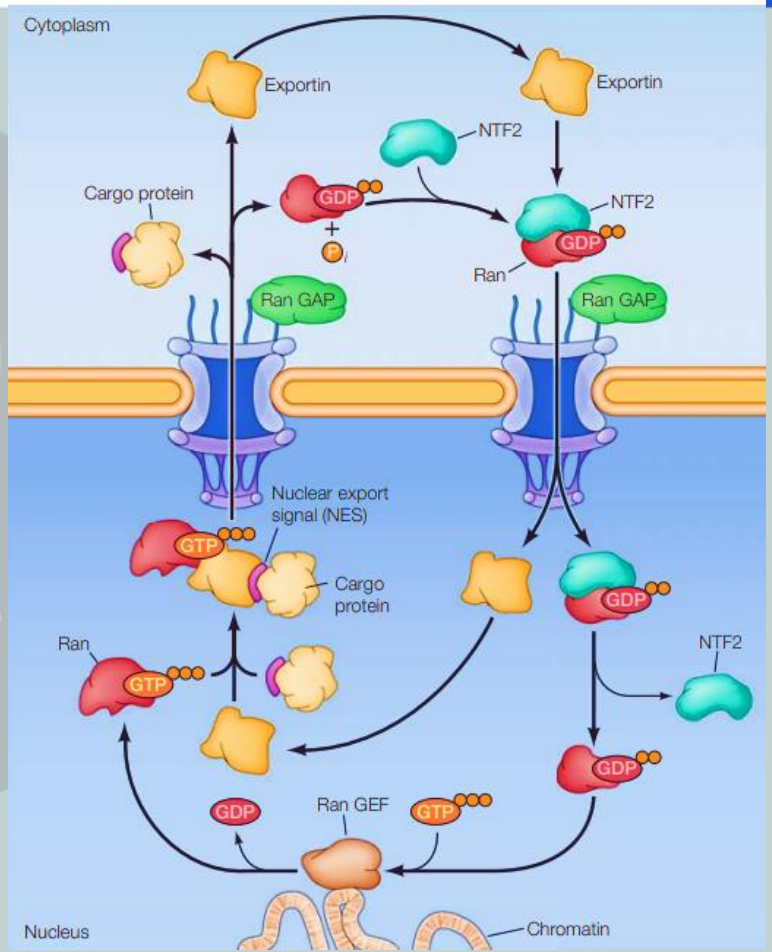


- The importin-Ran/GTP complex is re-exported through the nuclear pore and the GTPase-activating protein (Ran GAP) associated with cytoplasmic filaments stimulates hydrolysis of the GTP to GDP, releasing the importin.

- In the nucleus, Ran GEF (bound to chromatin) stimulates the exchange of GDP bound to Ran for GTP, leading to the conversion of Ran/GDP to Ran/GTP and maintaining a high concentration of Ran/GTP within the nucleus

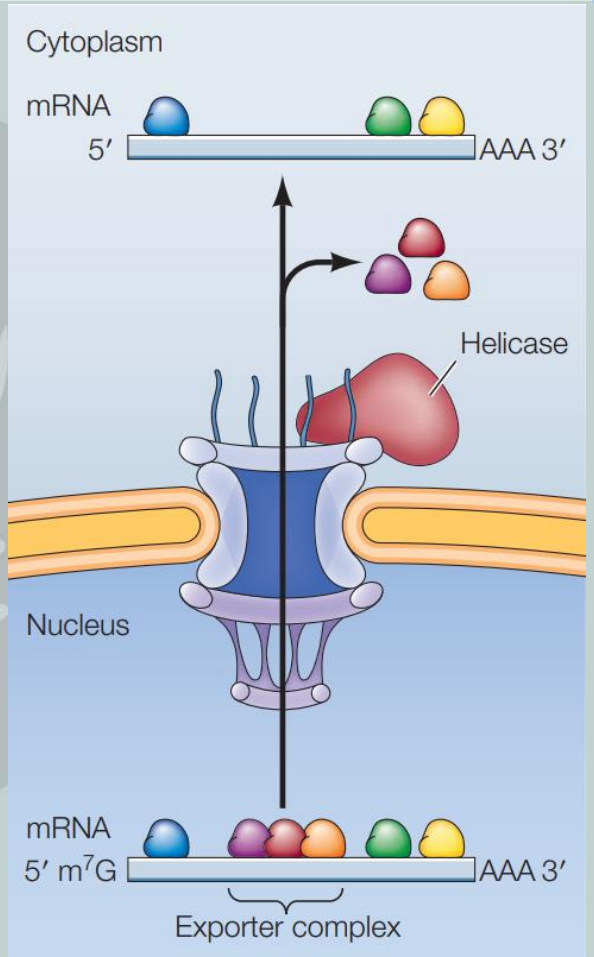
Nuclear export

- Complexes between cargo proteins bearing nuclear export signals (NES), exportins, and Ran/GTP form in the nucleus.
- Following transport through the nuclear pore complex, Ran GAP stimulates the hydrolysis of bound GTP, leading to formation of Ran/GDP and release of the cargo protein and exportin into the cytoplasm.
- Ran/GDP and the exportin are then returned to the nucleus. Ran/GTP is regenerated by Ran GEF bound to chromatin.



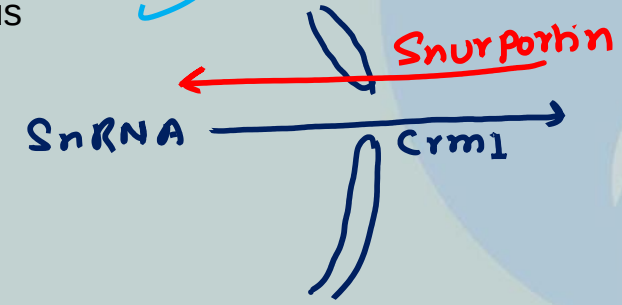
mRNA export

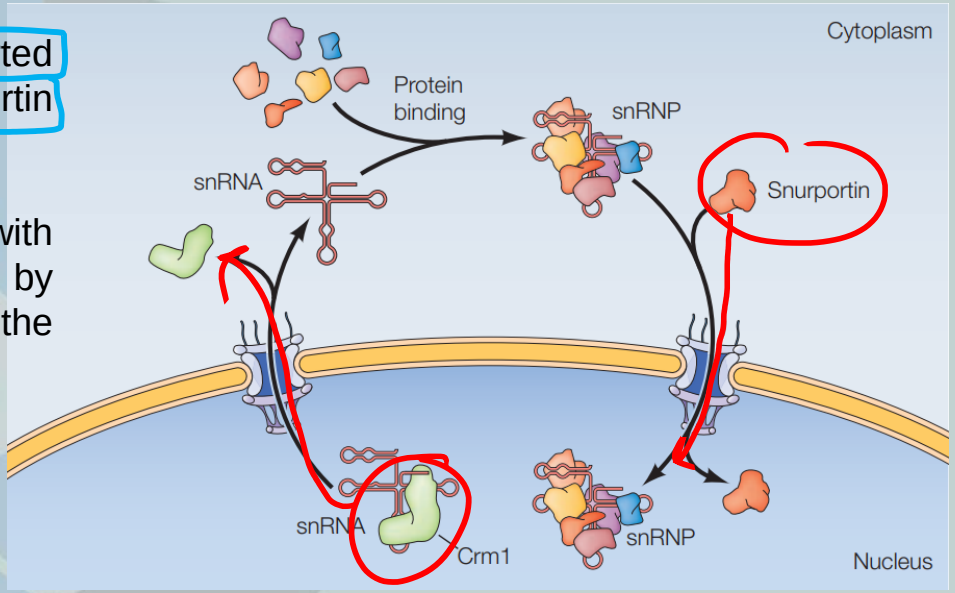
- mRNAs are bound by an exporter complex, which mediates their transport through the nuclear pore complex.
- A helicase associated with the cytoplasmic face of the nuclear pore complex releases the mRNA into the cytoplasm.



Transport of snRNAs between nucleus and cytoplasm

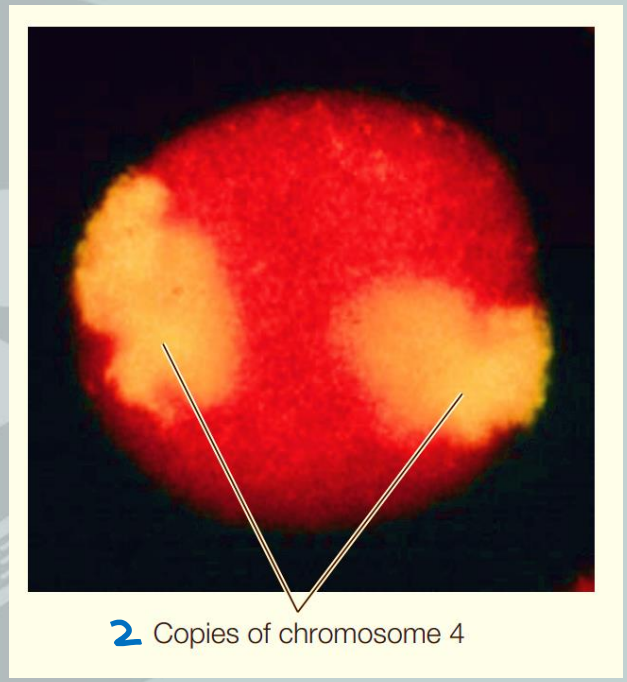
- Small nuclear RNAs (snRNAs) are initially exported from the nucleus to the cytoplasm by an exportin (Crm1).
- In the cytoplasm, the snRNAs associate with proteins to form snRNPs, which are recognized by an importin (snurportin) and transported back to the nucleus





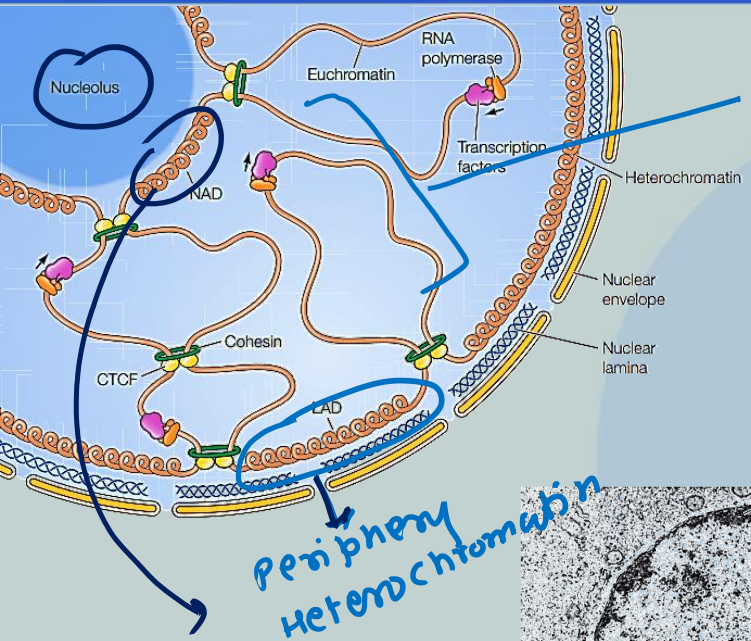
in 1885 by Carl Rabl, who proposed that each chromosome occupies a distinct territory

- Each chromosome was found to occupy a discrete region of the nucleus, called a chromosome territory



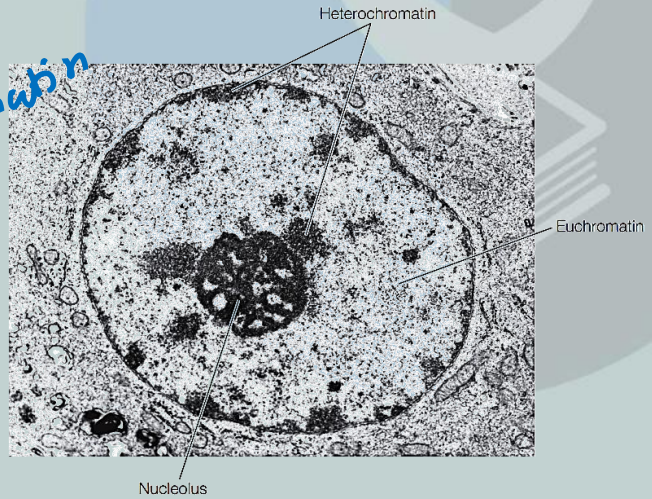
The two copies of chromosome 4, identified by yellow fluorescence, occupy distinct territories in the nucleus.

Nucleus



Euchromatin (in center)

Periphery Heterochromatin

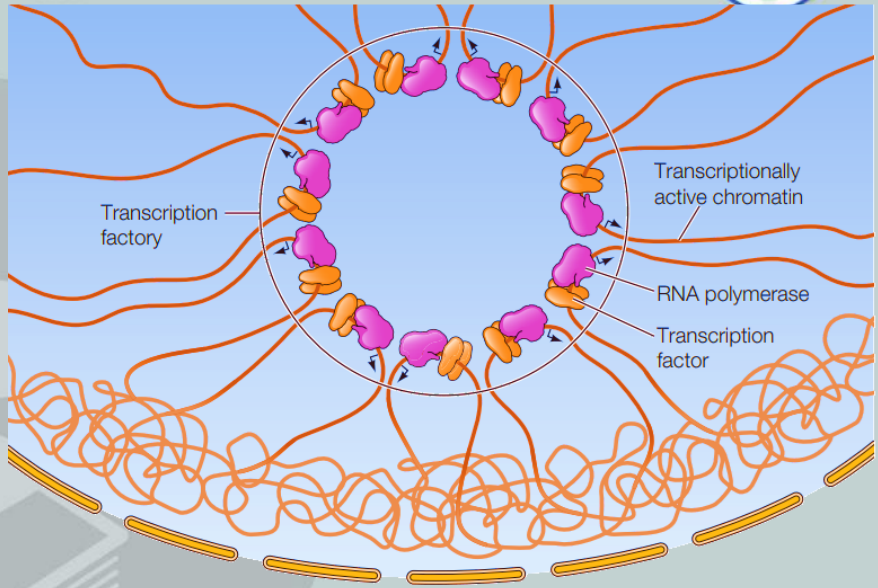


- The **euchromatin** is distributed **throughout** the **nucleus**.
- The **heterochromatin** is associated with the **nuclear envelope** and the **nucleolus**

Replication and transcription take place within clustered regions - Replication factories.

↳ contain DNA Pol.

Transcription also occurs at clustered sites -**transcription factories** that contain newly synthesized RNA and are highly enriched in active RNA polymerases and transcription factors.



Nuclear bodies

Nucleus contains a variety of discrete organelles, referred to as **nuclear bodies**

not enclosed by membranes but are instead maintained by protein–protein and protein–RNA interactions.

compartmentalize the nucleus and serve to concentrate proteins and RNAs that function in specific nuclear processes

Examples of Nuclear Bodies

Nuclear body	Number per nucleus	Function
Nucleolus	1–4	rRNA transcription, processing and ribosome assembly
Cajal body	0–10	snRNP assembly (Spliceosome)
Clastosome	0–3	Proteasomal proteolysis
Histone locus body	2–4	Transcription and processing of histone pre-mRNAs
Speckle	20–50	Storage of pre-mRNA splicing factors
PML body	10–30	Transcriptional regulation, DNA repair
Polycomb body	10–20	Gene silencing

Nucleolus

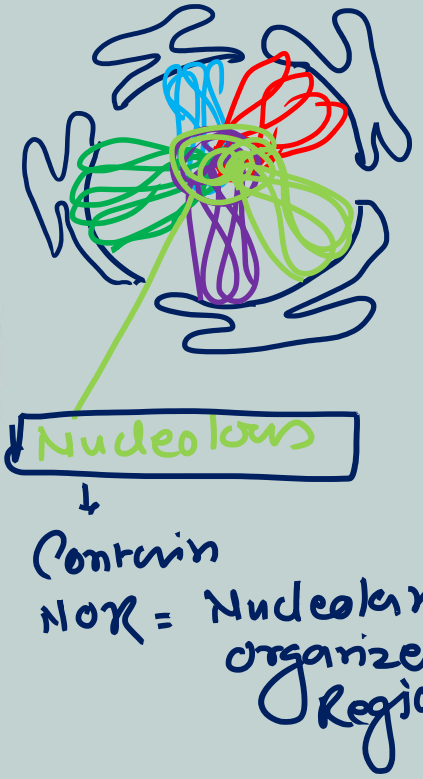
Introduction to Nucleolus-

Definition: Non-membrane bound structure inside the nucleus. → Site for Ribosome assembly

Formation: Different chromatin regions converge to form the nucleolar organizer region (NOR)

Chromosome No. 13, 14, 15, 21, 22

Function: Site for ribosomal RNA (rRNA) synthesis and ribosomal assembly.



Nucleolar Organizer Region (NOR)-

Chromosomes no. : 13, 14, 15, 21, 22

NOR contains: -

Housekeeping genes
- Actively transcribed genes ✓
- rRNA genes (40 copies per chromosome)- on each Chromosome

5 chromosome × 40 gene
= 200 gene

Total rRNA gene copies:

- Haploid organism: 200 - Diploid organism: 400 (200 × 2)

Ribosomal Assembly

- Ribosome structure-: Ribonucleoprotein = rRNA + Protein
- Small subunit: 40S ✓
- - Large subunit: 60S ✓

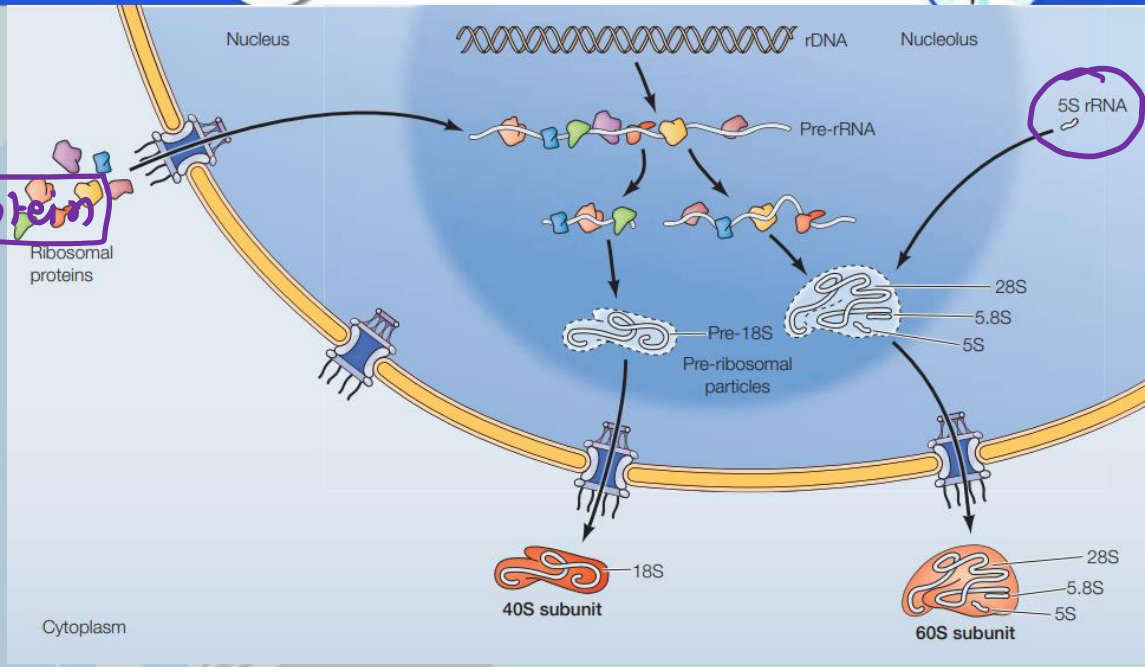
Components synthesized in nucleolus:

- 18S rRNA + 35 proteins (S1, S2, S3, etc.) =40 S

rRNA → Nucleolous

- 28S rRNA, 5.8S rRNA, 5S rRNA + 40 proteins (L1, L2, L3, etc) = 60 S

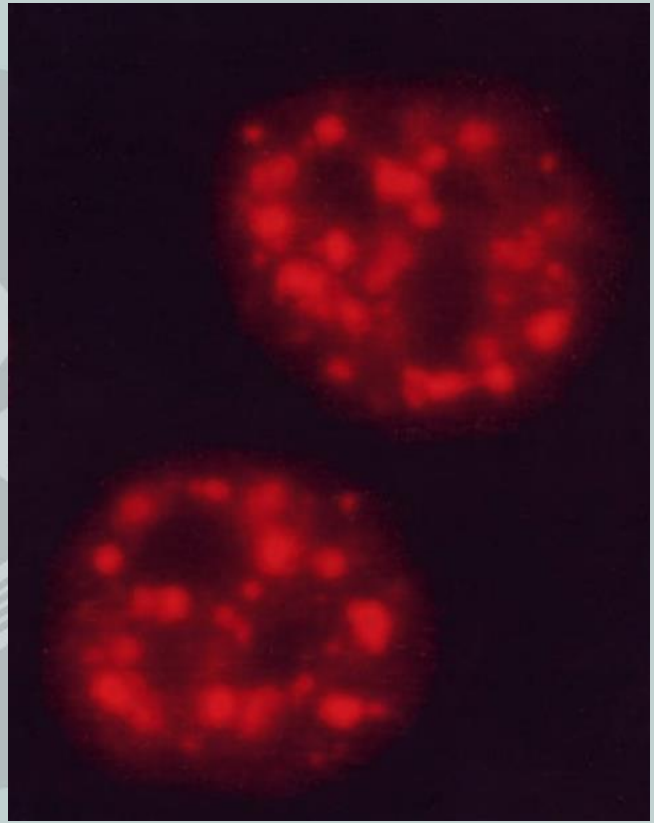
Synthesize out of Nucleolous



Nuclear Spackles:

- Site for splicing pre-mRNA into mRNA
- Working site for spliceosome-

Splicing site



Assembly of SnRPs (Assembly of Spliceosome)

Cajal Bodies:

- - Site for assembly of small nucleolar RNAs (snoRNAs) + proteins
- - Involved in splicing of hnRNA pre-mRNA

- Cajal bodies contain specific small Cajal body-specific RNAs (scaRNAs).

- The scaRNAs are related to the snoRNAs in nucleoli and similarly serve as guide RNAs to direct the ribose methylation and pseudouridylation of snRNAs in Cajal bodies

- Cajal bodies appear to play a role in assembly of telomerase

Promyelocytic Leukemia Bodies (PML Bodies)

- Dense regions in the nucleus- ~~Contents:~~
- High amount of transcription factors ✓
- Chromatin remodeling factors ✓

→ Transcriptionally active Region.

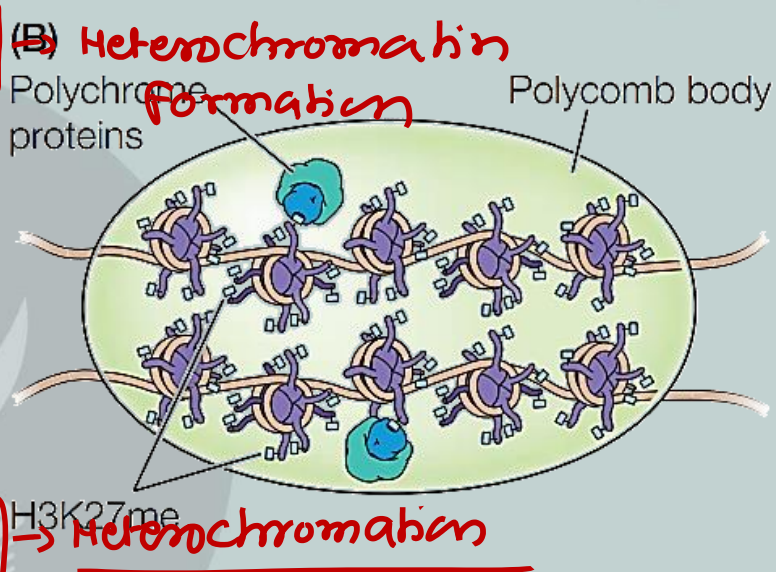
- **Function**: Conversion of heterochromatin to euchromatin for transcriptional activity.

Polycomb bodies contain clusters of repressed genes modified by methylation of histone H3 lysine 27 (H3K27me)

The Polycomb proteins consist of two complexes: one binds to methylated H3 lysine 27 residues and the other is an enzyme that methylates adjacent H3 lysine 27 residues.

As a result, methylation of H3 lysine 27 can spread to adjacent nucleosomes to generate domains of repressed chromatin.

Polycomb bodies are frequently associated with heterochromatin, consistent with their role in gene repression



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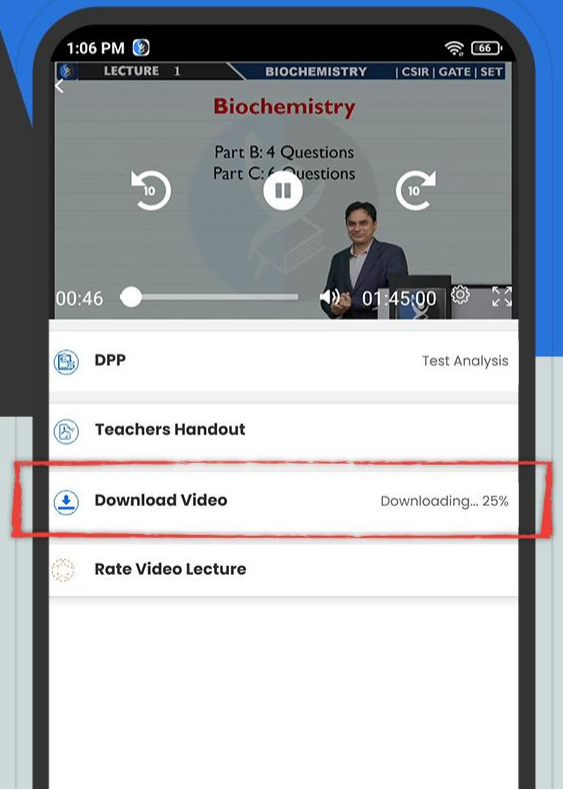

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